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(54) **Treatment of osteitis.**

(57) The invention provides a pharmaceutical composition for for filling into bone cavities comprising an aqueous paste formed from powdered calcium phosphate and an antibacterial substance, if necessary together with one or more binders. The antibacterial substance is preferably taurolidine and the calcium phosphate is preferably β-tricalcium phosphate.

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CHEMICAL COMPOSITIONS

This invention relates to a novel composition of use in the treatement of osteitis and osteomyelitis.

In the treatment of osteitis and osteomyelitis, where infection has led to necrosis of bone, it is essential that the necrotic bone (sequester) is removed from the infected site before further treatment can take place. Relatively large cavities are formed in this way and the regeneration of the bone tissue, including the spongeosa, is the primary objective of such further treatment. In our European Patent Application 48558 we have described resorbable gel formulations (which may contain antibacterial substances and other materials which assist bone regeneration and prevent re-infection) to be inserted in granulated form into such cavities to promote tissue growth.

In our above patent application we described gel formulations which contained up to about 20% by weight of calcium phosphate to provide calcium and phosphorus needed for bone formation. However, the granulated gel provided the main bulk of material required to fill the cavity, the voids between the gel granules permitting new tissue to grow into the mass which is gradually resorbed. Eventually, all the gel is resorbed and the cavity is filled by bone tissue. Even calcium phosphate is largely resorbed and regenerated in the physiological form in the new bone.

We have now found that an alternative composition for filling into bone cavities resulting from the surgical treatment of osteomyelitis and osteitis comprises an aqueous paste formed from powdered resorbable calcium phosphate and an antibacterial

substance resorbable together with one or more binders.

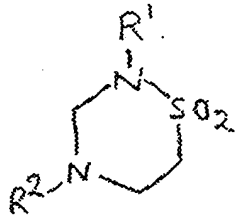
The calcium phosphate may be secondary or tertiary calcium phosphate or a more complex form such as hydroxyapatite. Other forms of calcium phosphate which can be used include tetra calcium phosphate and octa calcium phosphate. Tertiary calcium phosphate (i.e. tricalcium phosphate) is preferably in the β-form since this has been found to be more compatible with the growing bone cells and is more efficiently resorbed than the α-form. The particle size of the calcium phosphate is preferably above 200 microns, for example in the range 200-500 microns.

The preferred form of calcium phosphate is thus β-tricalcium phosphate in substantially pure form. The purity of the product can be determined by X-ray diffraction; however small quantities up to 2.3% of the α-form may be undetectable.

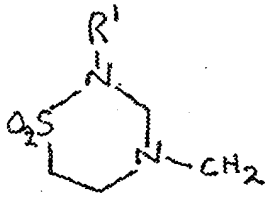
The antibacterial substances employed may be antibiotics and other microbiocidal or microbiostatic substances. In addition, further medicaments, for example analgesic agents may be used. In addition, the compositions can also contain other dissolved additives which promote healing of the wound and/or favourably influence the physical and biochemical properties of the composition. These are, for example, amino acids, sugar, polyhydric alcohols, common salt and others.

When the antibacterial substance is an antibiotic, it is preferably a broad spectrum antibiotic active against both gram-negative and gram-positive bacteria, for example, a β-lactam antibiotic such as a penicillin or cephalosporin, a tetracycline antibiotic, a macrolide antibiotic such as erythromycin, a polypeptide antibiotic such as bacitracin, novobiocin, or, more preferably, an aminoglycoside antibiotic such as streptomycin, neomycin, lincomycin, kanamycin,

vancomycin, gentamicin or sisomycin. Typical infecting bacteria include Staphylococcus aureus, Proteus, Pseudomonas, Streptococcus, E. coli, as well as Enterococci, Klebsiella and Staphylococcus albus. However, antibiotics are often contraindicated for use in surgical treatment, due to their tendency to produce resistant strains, and a preferred type of antibacterial substance is a methylol transfer agent, especially noxytiolin or, more preferably taurolidine or a close analogue thereof. Taurolidine is bis-(1,1-dioxo-perhydroxy-1,2,4-thiadiazin-4-yl)methane and this compound and its close analogues can be represented by the formula:



where R^1 is hydrogen or a methyl, ethyl, propyl, butyl or pentyl group and R^2 is hydrogen or a group



where R^1 has the above meaning. Where R^1 and R^2 are both hydrogen, the compound is the methylol transfer antibacterial taurultam.

The preferred active substances are broad spectrum antibiotics and methylol transfer agents such as taurolidine. Taurolidine and its analogues are active against both gram-negative and gram-positive organisms, as well as against the toxins produced by gram-negative bacteria.

The complex of elemental iodine and polyvinyl pyrrolidone may also be advantageously be used as a microbiocidal substance.

It is important that the binder for the calcium phosphate should be resorbable, so that it does not remain and give rise to tissue reactions after the remains of the composition has been resorbed.

In general, polyvinylpyrrolidone can be used as a binder in the formulations. A molecular weight in the range 200-30,000 is preferred. Kollidone 17 (sold by BASF) is one suitable form. Other useful binding agents include gelatin, e.g. edible gelatin, and dextran; the molecular weight of the dextran is preferably about 70,000. The binding agent will commonly comprise 2-10% by weight of the composition e.g. 4-6%.

The compositions of the invention will normally contain a relatively large amount of water, e.g. in the range 30-60%, preferably 40-50%. In general, the proportions of water and binding agent will depend on the consistency which is required. Relatively fluid compositions may be useful in that they can be introduced into the cavity via a post-operative drainage tube. In other instances, however, it may be preferable to pack the cavity with a more solid composition before closing the wound.

The quantity of calcium phosphate in the compositions will in general be above 30% and preferably about 40% by weight; they will normally contain up to 60% or even 70% by weight. This contrasts with the quantities of calcium phosphate incorporated into the gels as described in our above patent application which were always less than 20%.

The quantity of antibacterial substance may conveniently be in the range 0.5-5% by weight. Where taurolidine is used, it is preferably present in the range 1-4% by weight. In large cavities, 2% taurolidine may be sufficient; in small cavities,

e.g. in bones in the wrist, 4% by weight of taurolidine is preferred.

The following Examples are given by way of illustration only:-

Example 1	Weight %
β-Tricalcium phosphate (200 microns)	40,00
Taurolidine	4,00
Kollidone 17 PF	5,00
Distilled water	51,00

The above components are blended to give a relatively fluid suspension which can be administered via a drainage tube.

Example 2	Weight %
β-Tricalcium phosphate	50,00
Taurolidine	4,00
Kollidone 17 PF	5,00
Distilled water	41,00

The above components were blended together to yield a thick but still fluid paste which could be administered via a drainage tube and would remain in the cavity.

Example 3	Weight %
β-Tricalcium phosphate	50,00
Taurolidine	4,00
Kollidone 17 PF	5,00
Distilled water	31,00

The above components were blended together to give a moist powder for packing into a bone cavity.

Example 4	Weight %
Tricalcium phosphate	50,00
Taurolidine	4,00
Dextran 70,000	5,00
Distilled water	41,00

The above components were blended together

to give a relatively thick but fluid paste which could be introduced into a bone cavity via a drainage tube or directly, and would remain in the cavity.

Example 5	Weight %
Tricalcium phosphate	55,00
Taurolidine	4,00
Dextran 70,000	5,00
Distilled water	36,00

The above components were blended together to provide a plastic paste particularly suitable for direct application into an open cavity.

Example 6	Weight %
Tricalcium phosphate	48,00
Taurultam	4,00
Dextran 70,000	5,00
Distilled water	39,00

The above components were blended together to give a moist powder for direct application into an open cavity.

Example 7	Weight %
Dicalcium phosphate	50,00
Dextran 70,00	5,00
Taurolidine	4,00
Distilled water	41,00

The above components were blended together to give a rather fluid suspension.

Example 8	Weight %
Dicalcium phosphate	60,00
Dextran 70,000	5,00
Taurolidine	4,00
Distilled water	31,00

The above components were blended together to give a relatively thick paste.

CLAIMS:

1. A pharmaceutical composition for filling into bone cavities comprising an aqueous paste formed from powdered resorbable calcium phosphate and an antibacterial substance, together with one or more resorbable binders.

2. A composition as claimed in claim 1 in which the calcium phosphate is tricalcium phosphate.

3. A composition as claimed in in claim 2 in which the tricalcium phosphate is the β-form.

4. A composition as claimed in any of claims 1-3 which contains more than 30% by weight of calcium phosphate.

5. A composition as claimed in claim 4 which contains up to 70% by weight of calcium phosphate.

6. A composition as claimed in any of claims 1-5 in which the antibacterial substance is taurolidine or taurultam.

7. A composition as claimed in claim 6 which is fluid to enable introduction into said bone cavity via a drainage tube.

8. A composition as claimed in any of claims 1-7 in which polyvinylpyrrolidine, gelatin and/or dextran is present as the resorbable binder.

9. The use of a composition as claimed in claim 1 for filling a bone cavity in a human or animal subject.

10. The use as claimed in claim 9 in which the composition is introduced into said cavity via a drainage tube.

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PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

0147021
Application number
EP 84 30 7228

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
X	FR - A - 2 374 040 (H. SCHEICHER) * Page 2, lines 29-35; page 3, lines 36-40; page 4, lines 31-37; page 5, lines 1-3; claims 1,3,17,19 *	1,4,5,7,8	A 61 L 15/03 A 61 L 27/00 A 61 K 9/06 A 61 K 47/00 A 61 L 25/00
Y		2,3,6	
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Y	DE - A - 2 022 498 (FMC) * Page 4, lines 12-15; page 26, lines 14-23 *	2	
	--		
Y	GB - A - 2 032 777 (MERCK) * Page 2, lines 45-49, 101-105; page 4, lines 112-118; page 5, example 6 *	2	
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	./.		

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

A 61 L
A 61 K

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.

Claims searched completely: 1-8
Claims searched incompletely:
Claims not searched: 9-10
Reason for the limitation of the search: Method for treatment of the human or animal body by surgery or therapy (see article 52(4) of the European Patent Convention)

Place of search	Date of completion of the search	Examiner
The Hague	07-02-1985	PELTRE

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
Y	EP - A - 0 087 662 (MERCK) * Page 4, lines 7-17 * --	3	
DY	EP - A - 0 048 558 (GEISTLICH SOHNE) * Examples 6-12 * --	6	
A	FR - A - 2 350 826 (BATTELLE) * Example 7; claim 14 * --	1	TECHNICAL FIELDS SEARCHED (Int. Cl.4)
A	EP - A - 0 030 583 (OSTEO) --	1	
A	EP - A - 0 003 979 (BATTELLE) ----------	1	

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